August 26, 2003

Edwin L. Mongan
Manager, Environmental Stewardship
E.I. du Pont de Nemours & Company, Inc.
1007 Market Street
DuPont 6082
Wilmington, DE 19898

Dear Mr. Mongan:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Amine Heads Category posted on the ChemRTK HPV Challenge Program Web site on April 23, 2003. I commend E.I. du Pont de Nemours & Company, Inc. and Solutia, Inc. for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that duPont and Solutia advise the Agency, within 60 days of this posting on the Web site, of any modifications to their submission. Please send any electronic revisions or comments to the following addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
R. Gonzalez
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Amine Heads Category

Summary of EPA Comments

The sponsors, E. I. du Pont de Nemours & Company and Solutia, Inc., submitted a test plan and robust summaries to EPA for amine heads dated April 9, 2003. EPA posted the submission on the ChemRTK HPV Challenge Website on April 23, 2003. The category consists of two sponsored chemicals, 1,2-cyclohexanediamine (CAS No. 694-83-7) and 2-methyl-1,5-pentanediamine (CAS No. 15520-10-2). A third chemical, 1,6-hexanediamine (CAS No. 124-09-4), provides supporting data.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitted health effects data do not support inclusion of DCH in the category unless the submitter provides adequately supportive metabolism and/or other data. For ecological effects endpoints, the category approach is appropriate.

2. Physicochemical Properties. Adequate data are available for all endpoints except melting point for the purposes of the HPV Challenge Program.

3. Environmental Fate. The submitted data are adequate for the purposes of the HPV Challenge Program.

4. Health Effects. EPA believes that the data presented for HMD can be used to address data gaps only for MPMD and not for DCH. In the absence of more information, EPA believes that data gaps exist for genetic, repeated-dose, reproduction, and developmental toxicity endpoints for DCH.

5. Ecological Effects. Available data are adequate for all endpoints for the purposes of the HPV Challenge Program. The submitter needs to provide critical data elements missing from the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Amine Heads Challenge Submission

Category Definition

The submitter proposed the amine heads category consisting of the 6-carbon aliphatic diamines: 1,2-cyclohexanediamine (DCH), 2-methyl-1,5-pentanediamine (PMD or Dytek A), and 1,6-hexanediamine (HMD). HMD is not sponsored under the HPV Challenge Program but is included to provide support for the category. These three substances are by-products in the manufacture of HMD, which is used to produce nylon-6,6. "Amine heads" designates a mixture of lower boiling fractions (heads) of crude HMD containing DCH, MPMD, HMD and other compounds. The isolated "heads" may be discarded as waste, sold as a mixture, or further processed to purified forms of DCH and MPMD. The composition of the lower boiling amine heads varies, depending on the process details. A typical composition of the Solutia Amine Heads co-product is 25-55% DCH, 10-30% HMD, 10-20% 1,4-butanediamine, 7-20% 3-aminopropan-1-ol, 1-5% of a an aminocyclopentane derivative, 1-5% MPMD, and 10-20% water.

The title of this submission is misleading because the test plan addresses only the HPV chemicals, DCH and MPMD, and not the mixture known as "amine heads." The introductory Summary states, "...much of the material produced and handled is a mixture of these three major amines and a lesser quantity of the

material is the purified DCH or MPMD. Therefore, data on the crude mixture and data on the purified components are all relevant." Yet no further mention is made of characterizing mixtures. Because the commercial amine heads are complex and variable mixtures with many components, it is unlikely that the available data for the three chemicals will adequately characterize them.

The test plan does not discuss the ratio or variability of *cis* and *trans* isomers in purified DCH.

Category Justification

The submitter justifies grouping the listed chemicals into the Amine Heads category on the basis that they appear in the same process stream and have similar chemical structures, physicochemical and environmental fate characteristics, and environmental and mammalian toxicity.

The mammalian toxicity data support the use of HMD data to satisfy health effects data gaps for MPMD. However, the submitted data do not support inclusion of DCH in the category. None of the submitted data for DCH (other than acute toxicity and genetic toxicity) were adequate or comparable because the studies were of shorter duration, were conducted on mixtures containing DCH as a minor component (~ 7 to 31%), and/or showed different systemic effects. Given the absence of information on the metabolism of DCH (such as evidence of metabolism of DCH to relevant noncyclic metabolites) and the lack of data comparable with the other members, the available toxicological data do not support including DCH in the category.

For ecological effects the category approach is reasonable and the HMD data, with supportive ECOSAR values, can be extrapolated to DCH and MPMD.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for boiling point, vapor pressure, partition coefficient and water solubility are adequate for the purposes of the HPV Challenge Program.

Melting Point. The melting point value for MPMD (-50 to -60°C) appears significantly low in comparison to other diamines such as 1,2-propanediamine (mp -37°C); 1,3-propanediamine (mp -24°C); 1,4-butanediamine (mp 27°C); 1,5-pentanediamine (mp 9°C); and 1,6-hexanediamine (mp 41°C) (Ref. 1). In addition, the melting point for MPMD is given as a broad range (-50 to -60°C), that may indicate that test substance was impure. The submitter needs to verify its values or provide measured melting point data for MPMD following OECD guidelines. If the substance remains liquid below 0°C, then the value may be reported as < 0°C and further measurement is unnecessary.

For DCH, the submitter provided a melting point value of 2°C for the *cis* isomer and 15°C for the *trans* isomer, but did not provide one for the commercial mixture specified as the category member. The submitter needs to provide measured melting point data for commercial DCH following OECD guidelines. If the substance remains liquid below 0°C, then the value may be reported as < 0°C and further measurement is unnecessary.

Boiling Point. The submitter needs to specify whether 191°C is a boiling point for a DCH *cis-trans* mixture or for an individual isomer.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation, stability in water, biodegradation, and fugacity (transport and distribution) are adequate for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for all endpoints on HMD for the purposes of the HPV Challenge Program. EPA agrees that these data can be used to address data gaps for MPMD but not those for DCH (see Category Justification above). Thus, for DCH, EPA believes that data gaps exist for genetic toxicity, repeated-dose, reproduction, and developmental toxicity endpoints. The submitter needs to address a few deficiencies in the submitted robust summaries.

Repeated-Dose Toxicity. A 2-week inhalation assay on DCH that used methods similar to OECD Guideline 412 was not adequate to address this endpoint because of the short study duration. A 13-week gavage assay was also not adequate for DCH because only 6.8% DCH was present in the tested mixture. Additional testing is needed for DCH; OECD Guideline 422 would address this and reproduction and developmental toxicity endpoints (see below).

Genetic Toxicity. The data submitted on DCH for bacterial mutagenicity and *in vitro* chromosomal aberrations are not adequate because the tested mixture contained only 31% DCH. Additional testing for bacterial mutagenicity and chromosomal aberrations is needed for DCH.

Reproductive/Developmental Toxicity. No data are available for DCH and the submitted data for HMD are inappropriate for DCH. Additional testing is needed for DCH to address these endpoints which could be accomplished by testing under OECD TG 422 (see *Repeated -Dose Toxicity* above).

Ecological Effects (fish, invertebrates, and algae)

The submitted studies of HMD in *Pimephales promelas*, *Daphnia magna*, and *Selenastrum capricornutum* appear adequate to assess the potential toxicity of MPMD and DCH in fish, invertebrates, and algae, respectively, on the basis of the structural similarities between these two compounds. ECOSAR values were submitted for MPMD and DCH for acute toxicity in freshwater fish, Daphnia, and algae.

Although robust summaries were submitted for fish acute toxicity studies for DCH and MPMD, they were inadequate because of their brief duration (48 instead of 96 hours).

Specific Comments on the Robust Summaries

Health Effects

Acute Toxicity. The submitter needs to provide the magnitude of body weight effects in summaries for HMD and MPMD. It is unclear from the HMD robust summary whether gross pathology was conducted and whether any target organs were identified.

Repeated-Dose Toxicity. A summary for a 28-day oral toxicity study on MPMD had a gender error in the Results field relating to body weight effects–one statement indicates a non-significant decrease at 10,000 ppm in females and the other indicates significant decrease at 10,000 ppm also, in females.

Reproductive Toxicity. The submitter needs to provide information on whether or not a reduction in pup weights observed during lactation was statistically significant.

Ecological Effects

Fish. For the HMD study summary, the submitter needs to report dissolved oxygen and TOC.

Invertebrates and algae. For both endpoints on HMD, the submitter needs to report TOC and for algae, water hardness.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

References

1. Leung HW and Paustenbach DJ; (1990) J. Ind. Med. 18:717-35.

2. Aldrich Handbook of Fine Chemicals and Laboratory Equipment. 2003-2004. Milwaukee, WI: Aldrich Chemical Company., p. 567

3. Conlon DA;Yasuda N; (2001) Adv Synth Catal 343(1): 137-138.